INTERMEDIATES FOR THE PREPARATION OF ANALOGS OF HALICHONDRIN B

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

CROSS-REFERENCE TO RELATED APPLICATIONS

[This application claims priority under 35 U.S.C. §371 from international application PCT/US05/019669, filed Jun. 3, 2005, which claims priority to U.S. Provisional Patent Applications 60/576,642, filed Jun. 3, 2004, 60/626,769, filed Nov. 10, 2004, and 60/663,300, filed Mar. 18, 2005, the entire contents of each of which are hereby incorporated herein by reference.] *Notice: More than one reissue application has been filed for the reissue of U.S. Pat. No. 7,982,060. The reissue applications are Reissue application. Ser. No. 13/495,909, and the present application filed herewith. This application is a divisional reissue application of U.S. patent application Ser. No. 13/495,909, filed Jun. 13, 2012, which is a broadening reissue of U.S. Pat. No. 7,982,960, issued on Jul. 19, 2011, from U.S. patent application Ser. No. 11/628,396, which is the National Stage Entry of International Application No. PCT/US2005/019669, filed Jun. 3, 2005, which claims the benefit of priority of U.S. Provisional Application No. 60/576,642, filed on Jun. 3, 2004, U.S. Provisional Application No. 60/626,769, filed on Nov. 10, 2004, and U.S. Provisional Application No. 60/663,300, filed on Mar. 18, 2005, all of which are incorporated herein by reference in their entirety.*

TECHNICAL FIELD OF INVENTION

The present invention relates to compounds useful as intermediates in the synthesis of pharmaceutically active macrolide compounds.

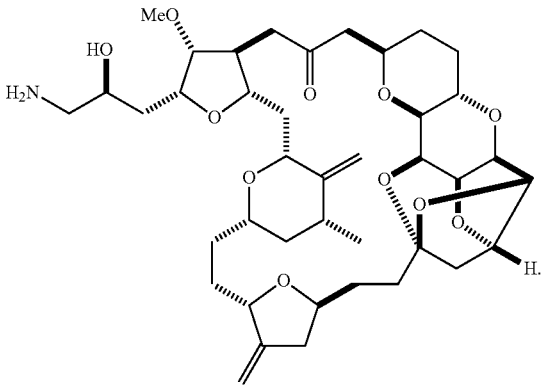
BACKGROUND OF THE INVENTION

The invention relates to pharmaceutically active macrolides, synthesis thereof and intermediates thereto. Halichondrin B is a potent anticancer agent originally isolated from the marine sponge Halichondria okadai, and subsequently found in Axinella sp., Phakellia carteri, and Lissondendryx sp. A total synthesis of Halichondrin B was published in 1992 (Aicher, T. D. et al., J. Am. Chem. Soc. 114: 3162-3164). Halichondrin B has demonstrated in vitro inhibition of tubulin polymerization, microtubule assembly, beta^s-tubulin crosslinking, GTP and vinblastine binding to tubulin, and tubulin-dependent GTP hydrolysis and has shown in vitro and in vivo anti-cancer properties. Accordingly, there is a need to develop synthetic methods for preparing analogs of Halichondrin B useful as anti-cancer agents.

SUMMARY OF THE INVENTION

As described herein, the present invention provides methods for preparing analogs of Halichondrin B having pharmaceutical activity, such as anticancer or antimitotic (mitosis-blocking) activity. These compounds include a compound of formula B-1939:

B-1939



These compounds are useful for treating cancer and other proliferative disorders including, but not limited to, melanoma, fibrosarcoma, leukemia, colon carcinoma, ovarian carcinoma, breast carcinoma, osteosarcoma, prostate carcinoma, and lung carcinoma. The present invention also provides synthetic intermediates useful for preparing said analogs of Halichondrin B.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

The methods and intermediates of the present invention are useful for preparing various analogs of Halichondrin B as described in, e.g. U.S. Pat. No. 6,365,759 and U.S. Pat. No. 6,469,182 the entirety of which are incorporated herein by reference. These Halichondrin B analogs are prepared generally by the assembly of three fragments F-1, F-2, and F-3, as shown by Scheme I below: